Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 3, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.03.060

FOCUS ISSUE: HYPERTROPHIC CARDIOMYOPATHY

Aortic Stiffness Is Increased in Hypertrophic Cardiomyopathy With Myocardial Fibrosis

Novel Insights in Vascular Function From Magnetic Resonance Imaging

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Objectives The aim of the study was to determine if patients with hypertrophic cardiomyopathy (HCM), both with and without myocardial fibrosis, have altered aortic stiffness as assessed by magnetic resonance imaging (MRI) pulse wave velocity (PWV) measurements.

Background Abnormal aortic stiffness implies an unfavorable prognosis and has been established in a variety of aortic diseases and ischemic cardiomyopathy. However, the relationship between aortic stiffness and HCM has not been studied previously.

Methods The study was institutional review board approved and Health Insurance Portability and Accountability Act of 1996 compliant. Velocity-encoded MRI was performed in 100 HCM and 35 normal control subjects. PWV was determined between the mid-ascending and -descending thoracic aorta. Delayed-enhancement MRI was acquired for identification of myocardial fibrosis.

Results Mean age was 52.4 years in HCM and 45.3 years in control subjects. The prevalence of myocardial fibrosis in HCM was 70%. PWV was significantly higher in HCM patients compared with control subjects (8.72 ± 5.83 m/s vs. 3.74 ± 0.86 m/s, $p < 0.0001$). PWV was higher (i.e., increased aortic stiffness) in HCM patients with myocardial fibrosis than in those without (9.66 ± 6.43 m/s vs. 6.51 ± 3.25 m/s, $p = 0.005$).

Conclusions Increased aortic stiffness, as indicated by increased PWV, is evident in HCM patients, and is more pronounced in those with myocardial fibrosis. Further, aortic stiffening may adversely affect left ventricular performance. In addition, increased aortic stiffness correlates with myocardial fibrosis, and may represent another potentially important parameter for risk stratification in HCM, warranting further study. (J Am Coll Cardiol 2009;54:255–62)

Hypertrophic cardiomyopathy (HCM) is a complex genetic cardiac disorder that has been a subject of intense scrutiny and investigation for 5 decades. It is the most common cause of sudden cardiac death in young people, particularly in athletes (1,2). As a result of the clinical and phenotypic heterogeneity of HCM, it is challenging to determine a subset of patients who will have a higher risk of sudden cardiac death and adverse prognosis. Myocardial fibrosis detected by delayed-enhancement magnetic resonance imaging (DE-MRI) is an adverse risk factor, as it represents a substrate for ventricular arrhythmias. There is an increased likelihood and frequency of ventricular arrhythmias and sudden cardiac death in those with myocardial fibrosis (3,4).

In recent years, increased emphasis has been placed on the association of aortic stiffness with aging, as well as a

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variety of cardiovascular diseases, including atherosclerosis, heart failure, hypertension, diabetes, and aortopathies (5,6). Aortic stiffness potentially may be compromised in HCM, as a result of neurohormonal disturbances, endothelial dysfunction, abnormal baroreceptor reflex in the left ventricle, and intrinsic aortic wall fibrosis. However, aortic stiffness has not been studied in patients with HCM.

Assessment of aortic stiffness with velocity-encoded magnetic resonance imaging (VENC-MRI) is an attractive and promising strategy as this measurement does not depend on the knowledge of central arterial pressure or

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Manuscript received January 14, 2009; revised manuscript received March 10, 2009, accepted March 23, 2009.

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Abbreviations and Acronyms

DE-MRI = delayed-enhancement magnetic resonance imaging
FOV = field of view
HCM = hypertrophic cardiomyopathy
LVOT = left ventricular outflow tract
MRI = magnetic resonance imaging/image
PWV = pulse wave velocity
TE = echo time
TR = repetition time
VENC-MRI = velocity-encoded magnetic resonance imaging/image

geometrical assumptions that may limit other measurement tools (7–10). The role of cardiac magnetic resonance imaging (MRI) in the evaluation of HCM has been well established in the precise assessment of left ventricular mass, function, and the evaluation of myocardial fibrosis (11,12). The addition of aortic stiffness measurements using pulse wave velocity (PWV) measurements may enhance the value of MRI in further characterization of HCM, and provide an important tool in risk stratification.

Therefore, the objective of the present study was to determine if patients with HCM, both with and without myocardial fibrosis, by DE-MRI have altered aortic stiffness as assessed by MRI PWV measurements.

Methods

This was a retrospective, single-institution study with approval from the local institutional review board for waiver of individual informed consent.

Patient population. One hundred consecutive patients with HCM and 35 normal control subjects were included in this study. Diagnosis of HCM was established based on standard clinical criteria using history, physical examination, electrocardiogram, and echocardiogram. Exclusion criteria were concomitant aortic diseases such as aortic coarctation, Marfan syndrome, and prior history of septal alcohol ablation or myectomy. The presence of left ventricular outflow tract (LVOT) obstruction was assessed by resting LVOT gradient using transthoracic echocardiography. Normal control subjects had no identified cardiac or aortic abnormalities.

MRI. Cardiac MRI was performed with a 1.5-T MRI scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). After scout imaging to locate the cardiac axes, electrocardiogram-triggered nonbreath-hold black blood prepared half Fourier acquisition in steady state images were acquired in the axial orientation for a total of 40 slices. The imaging parameters were: echo time (TE) = 20 ms; repetition time (TR) = 800 ms; refocusing flip angle = 160°; slice thickness = 6 mm; field of view in x axis (FOVx) = 240 to 360 mm; field of view in y axis (FOVy) = 300 to 380 mm; typical matrix size = 124 × 192; and typical acquired spatial resolution = 2.4 × 1.8 mm.

Velocity-encoded imaging was acquired using a breath-hold, retrospectively electrocardiogram-gated gradient echo pulse sequence at the level of the pulmonary trunk to measure through-plane flow in the mid-ascending and -descending aorta with the following parameters: TE = 3.1 ms; TR = 5.0 ms; flip angle = 30°; slice thickness = 6 mm; FOVx = 240 to 360 mm; FOVy = 300 to 380 mm; typical matrix size = 128 × 256; typical acquired spatial resolution = 2.3 × 1.3 mm; temporal resolution = 25 to 35 ms; and velocity encoding = 200 cm/s.

To assess the presence of myocardial fibrosis, delayed-enhancement images were acquired in contiguous short-axis, and 2-, 3-, and 4-chamber long-axis orientations, with a breath-hold inversion recovery spoiled gradient echo sequence: TE = 4 ms; TR = 8 ms; flip angle = 30°; bandwidth = 140 Hz/pixel; 23 k-space lines acquired every other R-R interval; FOVx = 260 to 360 mm; FOVy = 300 to 360 mm; typical matrix size = 152 × 256; and typical acquired spatial resolution = 2.0 × 1.3 mm. Images were acquired 15 to 20 min after intravenous injection of 0.2 mmol/kg gadolinium dimeglumine (Magnevist, Berlex Imaging, Wayne, New Jersey) during successive 8 to 10 s breath-holds. For each individual patient, the inversion time (range 225 to 275 ms) was optimized to null viable myocardium.

Image analysis. Using dedicated cardiovascular image analysis software (Argus, Siemens Medical Solutions), the contours of the mid-ascending and -descending aorta were drawn. The flow (in m/s) at these 2 levels was obtained from the velocity data of each voxel in all phases of the cardiac cycle. From the corresponding flow-time curves, the arrival of the foot of the pulse wave was measured as the point of interception of the linear extrapolation of the steep early systolic slope and the baseline. Multiplanar reconstructions of the axial half Fourier acquisition in steady state images were performed to measure the aortic path length. The centerline was drawn on a reconstructed sagittal view from the level of the mid-ascending aorta to the mid-descending aorta, corresponding to the same level where the VENC-MRI was acquired (Fig. 1). The PWV, assessed between the mid-ascending and -descending aorta, was calculated according to the following formula:

$$\mathrm{PWV} = \frac{\Delta x}{\Delta t}\ (\mathrm{m/s})$$

where Δ x was the aortic path length between the midascending and mid-descending aorta, and Δ t was the time delay between the arrival of the foot of the pulse wave at these levels (7,13).

The presence or absence of myocardial fibrosis was determined from DE-MRI slices obtained in the short-axis, and 2-, 3-, and 4-chamber views, without knowledge of the results of PWV measurements.

To determine intraobserver and interobserver reproducibility, the data of randomly selected patients (40 HCM and 20 control subjects) were reanalyzed by the same observer (T.B.) 4 weeks after the initial analysis, and by a second independent observer (P.R.), blinded to the initial results.

Statistical analysis. All statistical analyses were performed using the statistical software program (version 9.1, SAS

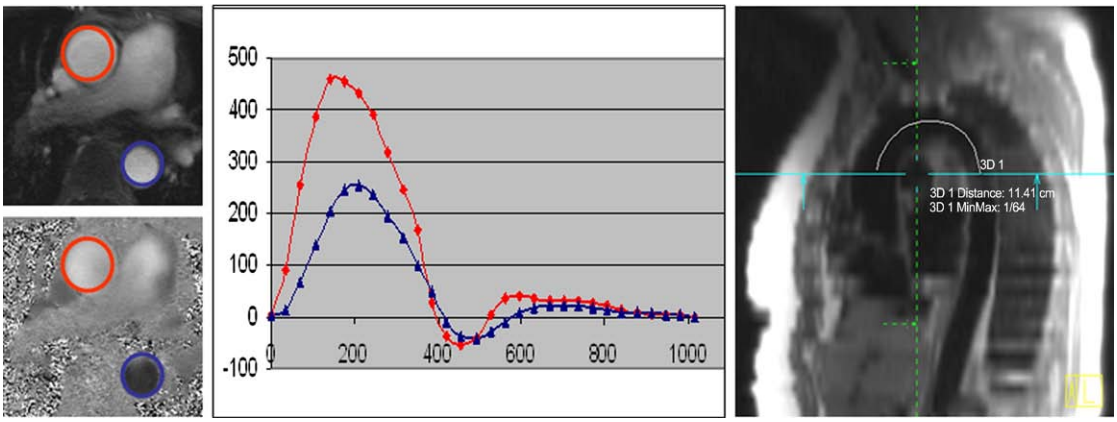

Figure 1 **Measurement of Time Delay Between Pulse Waves and Aortic Path Length**

(Left) Through-plane velocity-encoded magnetic resonance imaging at midascending **(red circles)** and mid-descending thoracic aorta **(blue circles)**. **(Middle)** Corresponding flow measurement at midascending **(red line)** and mid-descending thoracic aorta **(blue line)**. **(Right)** The measurement of aortic path length from a multiplanar reconstructed oblique sagittal view.

Institute, Cary, North Carolina). Continuous data were expressed as mean values and corresponding SDs, whereas dichotomous data were presented as numbers and percentages. Categorical variables were compared among the 3 patient groups using chi-square tests; continuous variables were compared using a 1-way analysis of variance. When the overall test was found to be significant ($p < 0.05$), the 3 pairwise comparisons were performed using Bonferroni adjustments to control the overall type I error rate. The analysis of covariance was used to demonstrate the difference in PWV among HCM patients and normal control subjects, adjusting for age. Further, the differences in PWV between HCM patients with and without fibrosis, and HCM patients with and without LVOT obstruction were analyzed by analysis of covariance, adjusting for age. Adjustments for the multiple comparisons involving fibrosis and LVOT were not made. Intraobserver and interobserver mean differences of PWV were tested for statistical significance using the Bland-Altman method (14). Further, the correlations between the PWV of the 2 measurements from the same observer and between the PWV from the 2 observers were evaluated. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics. Baseline characteristics and basic MRI parameters are shown in Tables 1 and 2. Mean age was

Table 1 **Characteristics of HCM Patients and Control Subjects**

	HCM Patients		Control Subjects (n = 35)	p Value
	Fibrosis (n = 70)	No Fibrosis (n = 30)		
Age (yrs)	51.7 ± 16.7	54.0 ± 14.5	45.3 ± 17.8	0.078
Men/women	46 (66)/24 (34)	17 (57)/13 (43)	19 (54)/16 (46)	0.462
Height (cm)	171.9 ± 11.5	171.5 ± 11.4	170.7 ± 11.6	0.904
Weight (kg)	86.2 ± 15.6	90.3 ± 22.2	90.9 ± 16.0	0.390
Body surface area (mm^2)*	2.0 ± 0.2	2.1 ± 0.3	2.1 ± 0.2	0.467
Systolic blood pressure (mm Hg)	120 ± 14	126 ± 14	120 ± 16	0.210
Diastolic blood pressure (mm Hg)	76 ± 14	78 ± 9	74 ± 12	0.454
Pulse pressure (mm Hg)	46 ± 15	48 ± 9	46 ± 12	0.759
Heart rate (beats/min)	65 ± 11†	70 ± 12	72 ± 10†	0.006
Medications				
Beta-blocker	52 (75.4)*†	20 (66.7)*	13 (37)†	0.001
Calcium-channel blocker	13 (18.8)	7 (23.3)	4 (11.4)	0.440
ACEI	5 (7.2)	3 (10.0)	4 (11.4)	0.760
ARB	2 (2.9)	4 (13.3)	4 (11.4)	0.112

Data are mean ± SD or n (%). *According to the formula: $\sqrt{}$ [height (cm) × weight (kg)/3,600]; significantly different pairs of groups (after Bonferroni correction) indicated by * and †.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HCM = hypertrophic cardiomyopathy.

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Table 2 MRI Parameters in HCM Patients and Control Subjects

	HCM Patients		Control Subjects	
	Fibrosis (n = 70)	No Fibrosis (n = 30)	(n = 35)	p Value
LVEDV (ml)	178.0 ± 50.7*	151.1 ± 42.6*	150.6 ± 42.0	0.010
LVESV (ml)	72.8 ± 32.5*	54.5 ± 21.3*	64.7 ± 21.2	0.014
LVEF (%)	60.6 ± 7.5*	65.1 ± 5.8*†	59.5 ± 5.5†	0.004
LV mass (g)	172.7 ± 67.0*	142.4 ± 52.9†	82.0 ± 14.2*†	<0.0001
Ascending aortic diameter (cm)	2.9 ± 0.3	2.9 ± 0.2	2.8 ± 0.4	0.106
Descending aortic diameter (cm)	2.2 ± 0.4	2.3 ± 0.3	2.1 ± 0.3	0.120
PWV (m/s)	9.66 ± 6.43*†	6.51 ± 3.25*	3.74 ± 0.86†	<0.0001

Significantly different pairs of groups (after Bonferroni correction) indicated by * and †.
HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MRI = magnetic resonance imaging; PWV = pulse wave velocity.

51.7 ± 16.7 years in HCM patients with fibrosis, 54.0 ± 14.5 years in HCM patients without fibrosis, and 45.3 ± 17.8 years in control subjects. The prevalence of myocardial fibrosis in HCM patients was 70%. LVOT obstruction (resting gradient ≥30 mm Hg) was present in 77%. There was no correlation between LVOT obstruction and myocardial fibrosis or ascending aortic diameters (p = 0.96 and p = 0.85, respectively).

Aortic PWV. The PWV could be determined in all patients and normal control subjects, with good quality velocity-encoded images and corresponding flow-time curves. The PWV, adjusted for age, was significantly greater in patients with HCM compared with normal control subjects (8.72 ± 5.83 m/s vs. 3.74 ± 0.86 m/s, p < 0.0001) (Fig. 2, Table 2). In addition, HCM patients with myocardial fibrosis had significantly higher PWV than HCM patients without myocardial fibrosis (9.66 ± 6.43 m/s vs. 6.51 ± 3.25 m/s, p = 0.005). Short-axis cine steady-state free-precession and DE-MRI, flow time curves, and PWV measurements for these 3 subsets are illustrated in Figures 3 to 5. However, there was no significant difference in PWV values between HCM patients with and without LVOT obstruction (p = 0.151).

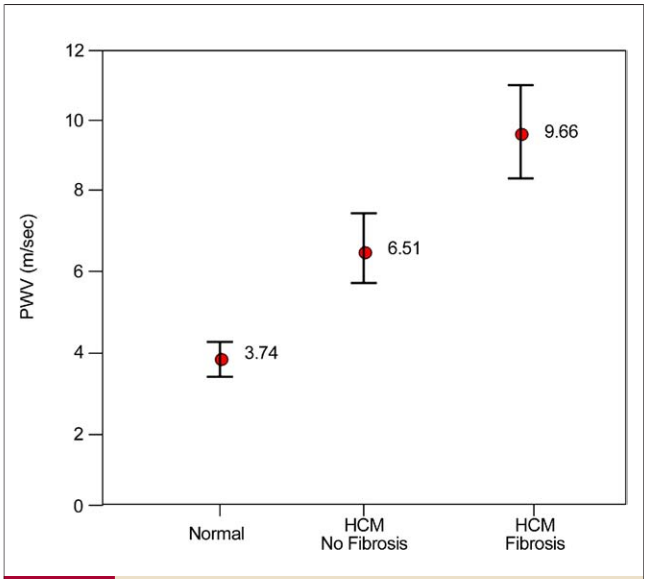

Figure 2 PWV in Control Subjects, HCM Patients Without Fibrosis, and HCM Patients With Fibrosis

The pulse wave velocity (PWV) (mean ± SD) in normal control subjects, hypertrophic cardiomyopathy (HCM) patients without myocardial fibrosis, and HCM patients with myocardial fibrosis was 3.74 ± 0.86 m/s, 6.51 ± 3.25 m/s, and 9.66 ± 6.43 m/s, respectively. **Circles** = mean; **whiskers** = 95% confidence intervals.

Reproducibility of PWV measurements. There was good intraobserver and interobserver reproducibility for the PWV measurements. The mean PWV ± SD values were 7.09 ± 4.05 m/s and 7.07 ± 4.07 m/s (r = 0.99) for the first observer (T.B.) in the initial analysis and 4 weeks later, respectively, and 7.31 ± 4.27 m/s (r = 0.97) for the second observer (P.R.) in the initial analysis. Using the Bland-Altman method, intraobserver mean differences for 2 measurements of PWV were 0.03 ± 0.48 (p = 0.64), and interobserver mean differences were 0.19 ± 1.10 (p = 0.136), respectively (Fig. 6).

Discussion

This study is the first to demonstrate abnormal aortic stiffness in HCM patients as indicated by altered PWV measurements. In addition, the abnormality was more pronounced in the presence of myocardial fibrosis. Increased aortic stiffness may affect ventriculo-vascular coupling, and, as a consequence, left ventricular performance. Abnormal vascular function may be a novel parameter for risk stratification in HCM patients.

Aortic stiffness. There is increasing evidence to suggest that abnormalities in aortic stiffness correlate with aging and pathologic states such as atherosclerosis, congestive heart failure, hypertension, diabetes, and aortic disorders such as Marfan syndrome, and aortic aneurysm (10,15–18). In addition, central arterial stiffness has been highlighted as an independent prognosticator of cardiovascular events in some populations (6,19–21).

A wide variety of methods have been proposed for the evaluation of aortic stiffness (22,23). Most of these techniques require knowledge of area and pressure, the latter obtained directly only by invasive means. Noninvasive methods rely on brachial pressure measured by a sphygmo-

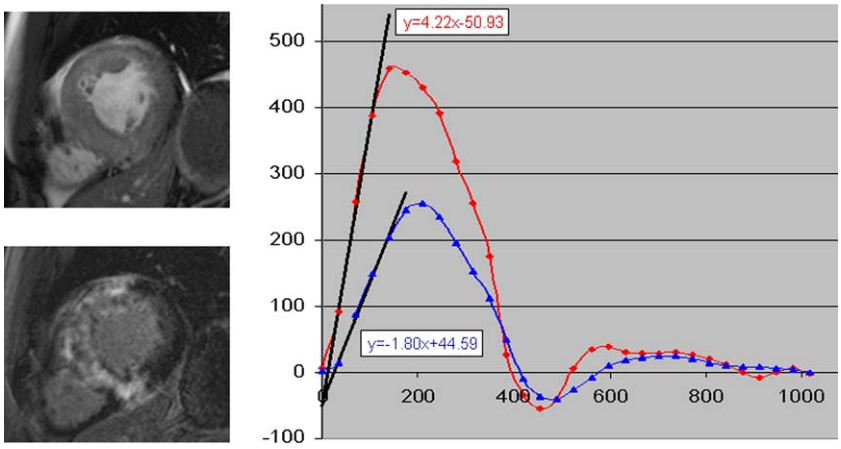

Figure 3 **PWV Measurement in an HCM Patient With Myocardial Fibrosis**

(Left) Steady-state free-precession static cine image from end-diastole **(top)** demonstrates moderate septal hypertrophy, along with patchy, midmyocardial delayed enhancement in the septum **(bottom)**, consistent with myocardial fibrosis. **(Right)** Flow measurement at midascending **(red line)** and mid-descending thoracic aorta **(blue line)**. The measurements of arrival time at midascending and mid-descending aorta are 12.1 and 24.8 ms, respectively. The aortic path length is 12.80 cm. The calculated PWV is: [12.80 cm/(24.8 − 12.1 ms)] = 10.08 m/s. Abbreviations as in Figure 2.

manometer acting as a surrogate of central aortic pressure. This technique is a fairly imprecise approximation, as pressure amplification may be a significant hindrance to directly equate peripheral to central pressure (19,24). Further, this technique assumes lack of hemodynamically significant narrowings or obstruction between the central and peripheral arterial bed. In addition, cardiovascular risk correlates better to central rather than peripheral pressure (19,25).

PWV is a well-accepted index of arterial stiffness with high reproducibility, and, moreover, without the central pressure assumption (20). The principle that a pulse wave travels faster in a rigid than a distensible tube enables estimation of regional mechanical wall properties. The PWV assessed by ultrasound or tonometry has inherent limitations, such as the estimation of propagation distance of the traveling pulse from the surface, and the limited acoustic window for the assessment of deep arteries such as the aorta (26). In contrast, MRI can display the anatomy of vessels in any plane, and velocity-encoded sequences can noninvasively measure blood flow in any direction or orien-

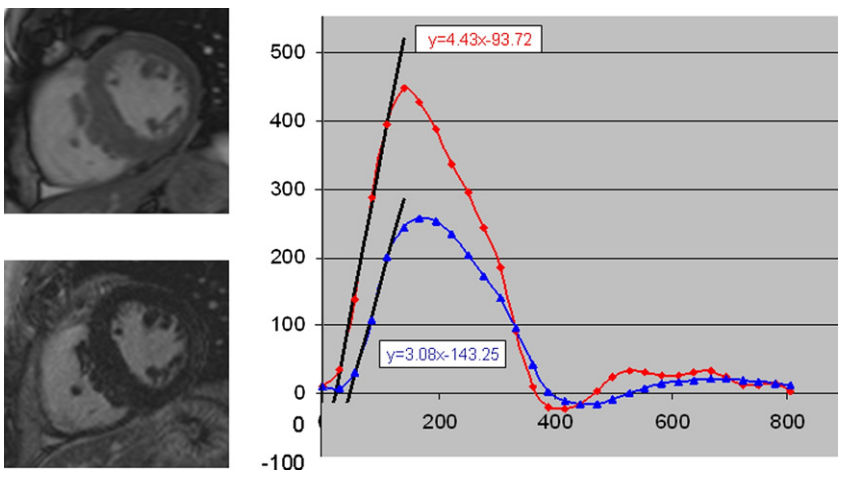

Figure 4 **PWV Measurement in an HCM Patient Without Myocardial Fibrosis**

(Left) Steady-state free-precession static cine image from end-diastole demonstrates mild septal hypertrophy **(top)**. There is no delayed enhancement in the hypertrophied region, implying absence of myocardial fibrosis **(bottom)**. **(Right)** Flow measurement at midascending **(red line)** and mid-descending thoracic aorta **(blue line)**. The measurements of arrival time at midascending and mid-descending aorta are 21.2 and 46.5 ms, respectively. The aortic path length is 12.84 cm. The calculated PWV is: [12.84 cm/(46.5 − 21.2 ms)] = 5.08 m/s. Abbreviations as in Figure 2.

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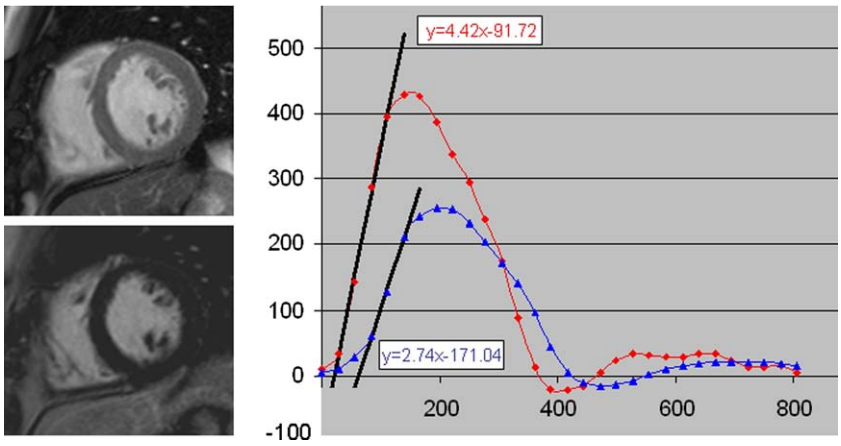

Figure 5 PWV Measurement in a Normal Control Subject

(Left) Steady-state free-precession static cine image from end-diastole demonstrates normal wall thickness **(top)**, while delayed enhancement imaging demonstrates absence of myocardial fibrosis **(bottom)**. **(Right)** Flow measurement at midascending **(red line)** and mid-descending thoracic aorta **(blue line)**. The measurements of arrival time at midascending and mid-descending aorta are 20.8 and 62.4 ms, respectively. The aortic path length is 12.89 cm. The calculated pulse wave velocity (PWV) is: [12.89 cm/(62.4 − 20.8 ms)] = 3.10 m/s.

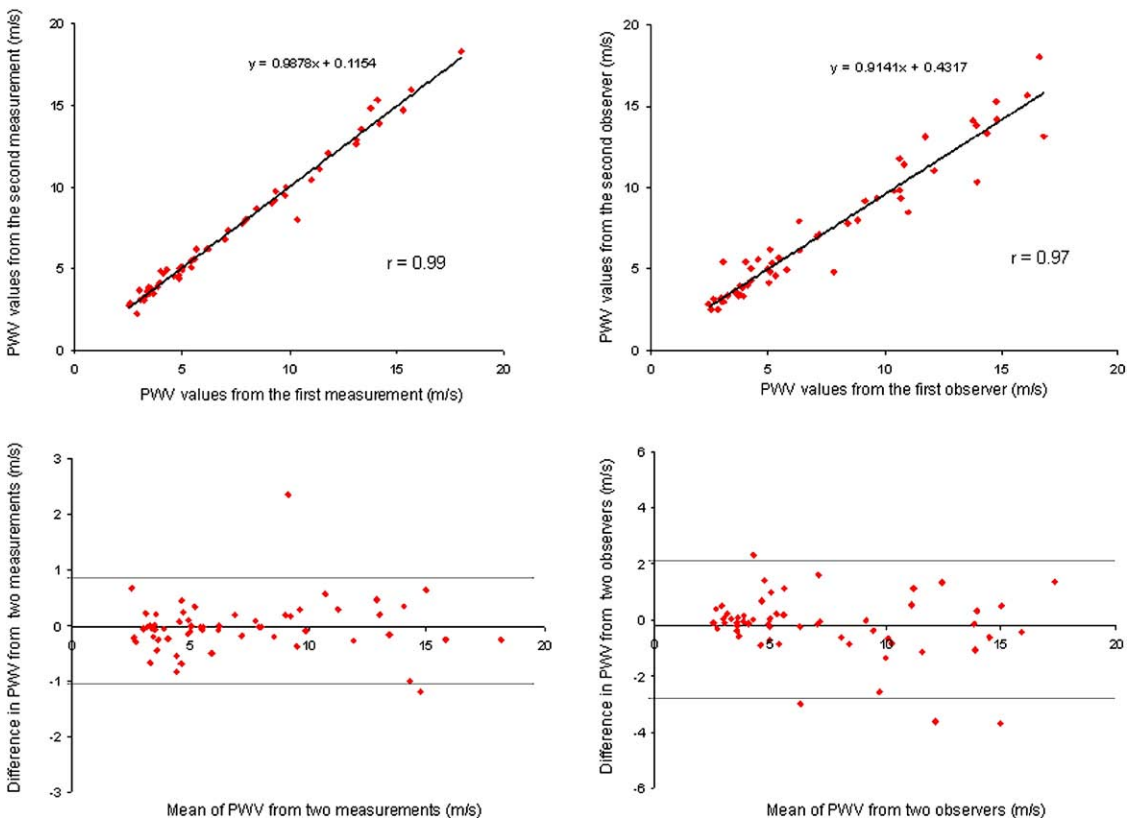

Figure 6 Intraobserver and Interobserver Reproducibility

(Top) The correlation between the pulse wave velocity (PWV) measurements between 2 measurements in the same observer and between 2 independent observers (n = 60 for both). **(Bottom)** Bland-Altman plots of the PWV measurements between 2 measurements in the same observer and between 2 independent observers (n = 60 for both).

tation. The PWV calculated by VENC-MRI does not depend on knowledge of central arterial pressure or geometrical assumptions that may limit other established measurement tools (7–10,27).

Etiology of abnormal aortic stiffness. In spite of emerging evidence of abnormal aortic stiffness in a variety of cardiovascular diseases, vascular stiffness has not previously been studied in the HCM population. In our study, patients with HCM manifested a significantly higher PWV, indicating increased aortic stiffness, and PWV was more pronounced in the presence of myocardial fibrosis. The precise etiology for this vascular dysfunction is uncertain, but potential contributors include neurohormonal disturbances, endothelial dysfunction, abnormal left ventricular baroreceptor response, and intrinsic aortic wall fibrosis specific to HCM. Neurohormonal changes may result from elevated left ventricular pressure. An activated renin-angiotensin-aldosterone system and norepinephrine contribute to vasoconstriction and sodium retention in the vascular wall (17,28). Further, the effect of angiotensin II may result in vascular wall structure changes (29). Endothelial dysfunction affects pulsatile pressure buffering and vasodilation of the arterial system through the elaboration of vasoactive substances, such as endothelial-derived relaxing factor (22,29). HCM patients also may have abnormal left ventricular baroreceptor stimulation, resulting in inappropriate vasodilation (30). Vasoconstrictor response during exercise has been shown to be inhibited or reversed in patients with severe aortic stenosis, potentially from abnormal reflex in left ventricular baroreceptor stimulation (31). Finally, intrinsic aortic wall fibrosis in HCM may be an alternative contributor to aortic stiffening; this remains an intriguing consideration given the known interstitial myocardial fibrosis present in a subset of HCM patients, but was not directly evaluated in this study. In addition, the association of increased aortic stiffness with HCM and myocardial fibrosis may reflect the severity of myocardial involvement and left ventricular performance (32).

Effects of impaired aortic stiffness. Increased aortic stiffness is an important pathophysiologic feature that leads to augmented systolic pressure and attenuated diastolic pressure, resulting in elevated pulse pressure (19,33). Higher pulse pressure may be responsible for arterial medial damage, pressure overload, and left ventricular hypertrophy (34–36). Increased left ventricular afterload causes stiffening of the left ventricle and increased wall tension, which adversely alters ventriculo-vascular coupling and detrimentally impacts on ventricular performance and diastolic relaxation (37). As well, lower diastolic pressure induces a reduction of the coronary perfusion. Stiffening of the aorta may contribute to limited exercise capacity via the inability to generate adequate cardiac output and reduction in skeletal muscle perfusion during exercise (17,38). As further evidence, the relationship between ventriculo-vascular stiffening index, assessed by MRI, and maximum oxygen consumption has been demonstrated in patients with HCM (39).

Abnormal vascular function may relate to hypotensive response during exercise, one of the risk factors for sudden cardiac death. It had been assumed that exercise-induced hypotension was related to the inability to maintain stroke volume during tachycardia. However, an invasive hemodynamic study demonstrated that hypotension was related to a fall in vascular resistance from an abnormal vascular response, and occurred despite an appropriate rise in cardiac index (30). Impaired vascular function, as indicated by abnormal PWV, may reflect this abnormal vascular response. This hypothesis, however, requires a further comprehensive study.

Clinical implication. As increased aortic stiffness leads to detrimental consequences on left ventricular performance and cardiovascular outcomes, this parameter may become an integral part of clinical risk stratification. Abnormal aortic stiffness in the already stiffening hypertrophic ventricle potentially leads to an even stiffer ventricle and development of symptoms. In addition to the previously established role of MRI in patients with HCM, PWV measurement with VENC-MRI may provide further information on vascular stiffness. This addition potentially enhances the already comprehensive role of MRI in the evaluation of HCM, which cannot be provided by any other single imaging modality.

Future direction. This study introduces a vascular element to this complex cardiomyopathy. The cause of abnormal aortic stiffness, its relationship with other traditional risk markers such as left ventricular thickness and mass, and the impact on clinical outcomes warrant further investigation.

Conclusions

In addition to well-established myocardial abnormalities, HCM is also associated with abnormal aortic stiffness, particularly in the presence of myocardial fibrosis. This novel parameter may become a complementary component in risk stratification of HCM patients.

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Key Words: aortic stiffness ■ pulse wave velocity ■ hypertrophic cardiomyopathy ■ myocardial fibrosis ■ magnetic resonance imaging.